

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 122 233 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
08.08.2001 Bulletin 2001/32

(51) Int Cl.7: **C07C 35/08, A61K 7/16,**
A23L 1/22

(21) Application number: **01400267.9**

(22) Date of filing: **02.02.2001**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

- Nakatsu, Tetsuo
Chappaqua, NY 10514 (US)
- Ishizaki, Takero
Iwata, Shizuoka 438-0077 (JP)
- Lupo, Andrew T., Jr.
Emerson, NJ 07630 (US)

(30) Priority: **04.02.2000 US 498592**
28.02.2000 US 514554

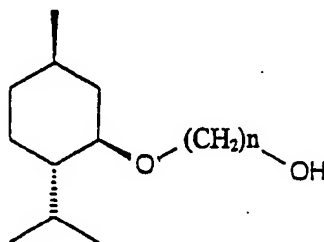
(71) Applicant: **Takasago International Corporation**
Tokyo (JP)

(72) Inventors:
• **Green, Carter B.**
Stony Point, NY 10980 (US)

(74) Representative: **Uchida, Kenji et al**
S.A. Fedit-Loriot et Autres Conseils en Propriété
Industrielle,
38, avenue Hoche
75008 Paris (FR)

(54) **A (1'R, 2'S, 5'R)-3-l-menthoxyalkan-1-ol cooling sensate**

(57) A cooling sensate compound having the general formula (I):



(I)

where n is an integer from 2 to 6. The compound is effective in imparting a refreshing and cooling sensation of long duration. A cooling sensate composition having the general formula (I) is used in a variety of formulations to impart the refreshing and cooling sensation. These cooling sensates are useful in a variety of consumer products including mouth formulations, food products and toiletries.

EP 1 122 233 A1

Description

[0001] The present invention relates to enantiomeric menthoxyalkan-1-ol compounds which function as cooling sensates. These compounds are useful as fragrance and flavor compounds in products such as toothpastes, skin lotions and hard candies and other confections.

[0002] Substances giving a physiologically cooling and/or refreshing feeling to the human skin or membranes, in particular to the membranes in the mouth, nose, throat, are well known. A representative example is *l*-menthol. *L*-menthol is widely used as a flavor substance which imparts a desirable cooling and/or refreshing feeling. *L*-menthol is widely used in oral formulations, such as toothpaste and chewing gums; in food and beverage products, such as sherbet and hard candy; and in toiletry products, such as cosmetics and eye pack materials. However, *l*-menthol has a strong minty smell and is also volatile. Although *l*-menthol has a strong cooling and/or refreshing effect, the effect is not long-lasting.

[0003] Other compounds having an effect similar to that of *l*-menthol are known. For example, 3-substituted-*p*-menthane compounds (Japanese Laid Open Patent Number 47-16,647, Japanese Laid Open Patent Number 47-16,649, British Patent Number 1,315,626), *N*-substituted-*p*-menthane-3-carboxamide compounds (Japanese Laid Open Patent Number 47-16,648), paramenthanediol compounds (Japanese Laid Open Patent Number 47-16,650), and 3-*l*-menthoxypropane-1, 2-diol (Japanese Examined Patent Number 61-48,813, US Patent 4,459,425) are disclosed which have an effect similar to that of *l*-menthol. Furthermore Japanese Laid Open Patent Number 7-82,200 discloses (2*R*)-3-((1'*R*, 2'*S*, 5'*R*)-[5'-methyl-2'-(1'-methylethyl) cyclohexyl] oxy)-1,2-propanediol.

[0004] Among these compounds, the 3-*l*-menthoxypropane-1,2-diol compound has a low volatility, is almost odorless, and has an excellent cooling effect. Because 3-*l*-menthoxypropane-1,2-diol does not have an effect on the aroma or flavor of the product, it is widely used in food and beverage products and in cosmetics.

[0005] British Patent Number 1,315,626 discloses that compounds having a *p*-menthane framework exist in *cis* form or *trans* forms. The compounds having an equatorial orientation have a stronger cooling and/or refreshing effect compared to the same compounds having an axial orientation, and thus are preferred. For example, 3-(2'-hydroxyethoxy)-*p*-menthane and 3-(2'-hydroxy-*n*-propyloxy)-*p*-menthane have been disclosed. However, there is no disclosure regarding the relation between the absolute stereochemistry of these compounds and the cool/refreshing feeling effect. While the British Patent does disclose that the *d*-form has, in most cases, a greater physiological cooling effect, there is no discussion of any preferred absolute configuration. The reference only notes that four geometric isomers arise from substitution at the 3-position of the basic *p*-menthane structure, and that for each of these geometric isomers, there are a number of optical isomers.

[0006] In recent years, consumer preferences for food and beverage products in as well as cosmetic products have become more varied. There is an increasing desire for development of food and/or beverage products as well as cosmetic products that provide cooling and/or refreshing effects, or similar unique type flavor impressions.

[0007] In light of the above, it is an object of the present invention to overcome the limitations of the prior art.

[0008] The present inventors have discovered through intensive study, that enantiomeric compounds having a *l*-menthane framework possess unexpectedly superior and longer lasting cooling sensate effects. The present invention was based on this finding.

[0009] It is an object of the present invention to provide cooling sensate compounds that provide long lasting cooling and refreshing effects.

[0010] It is another object of the present invention to provide cooling sensate compositions that are long lasting in effect.

[0011] It is another object of the present invention to provide a tooth paste containing a cooling sensate that is refreshing, cool and long lasting.

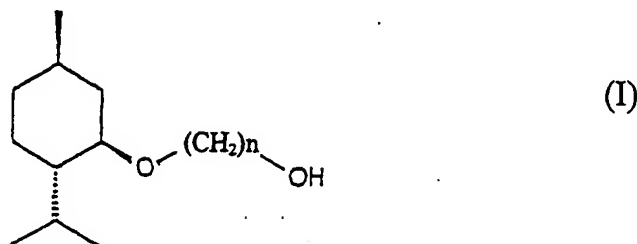
[0012] It is another object of the present invention to provide mouth formulation products using at least one compound of the present invention as a cooling sensate including mouth washes, a toothpaste, a tooth gel, cough drops, nebulizers, inhalants and other related products.

[0013] It is another object of the present invention to provide food products using at least one compound of the present invention as a cooling sensate including fruit juices, fruit wines, dairy drinks, carbonated drinks, a sports beverage, an ice cream, a sherbet, an ice candy, a jelly, a hard candy, a chewing gum, a bubble gum, a pressed mint tablet and related products.

[0014] It is another object of the present invention to provide a cooling sensate composition including an enantiomeric compound having a *l*-menthane framework along with at least one additional sensate compound to give rise to additional novel sensate effects.

[0015] It is another object of the present invention to provide toiletry products using at least one compound of the present invention as a cooling sensate including a nebulizer, a perfume, eau de toilette, lotion, a cologne, milky lotion, facial packs, hair care products, soap, antiperspirants, deodorizers, after shave lotions, a hand cream, a shampoo and other related products.

[0016] Briefly stated the present invention relates to a (1'R, 2'S, 5'R)-3- ℓ -menthoxyalkan-1-ol represented by the following formula (I).



wherein n is an integer from 2 to 6.

[0017] The present invention has a cooling and refreshing effect when in contact with human skin or membranes, and is useful as a flavor compound. The present invention further relates to oral formulations, food or beverage products, or toiletry products which contain a (1'R, 2'S, 5'R)-3- ℓ -menthoxyalkan-1-ol represented by the above formula (I).

[0018] According to an embodiment of the present invention, a cooling sensate comprises the enantiomer (1'R, 2'S, 5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol.

[0019] According to another embodiment of the present invention, a cooling sensate comprises the enantiomer (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol.

[0020] According to another embodiment of the present invention, a cooling sensate comprises the enantiomer (1'R, 2'S, 5'R)-4-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol.

[0021] According to another embodiment of the present invention, a mouth formulation comprises at least one of the enantiomers of the present invention in addition to relevant additives and other ingredients.

[0022] According to another embodiment of the present invention, a flavor formulation comprises at least one of the enantiomers of the present invention in addition to relevant additives and other ingredients.

[0023] According to another embodiment of the present invention, a food or beverage formulation comprises at least one of the enantiomers of the present invention in addition to relevant additives and other ingredients.

[0024] The above, and other objects, features and advantages of the present invention will become apparent from the following description of preferred embodiments and comparative examples.

[0025] The present inventors have discerned that among the known compounds which have a cooling and/or refreshing effect, such as menthoxypropan-1,2-diol, there is a common characteristic of having a p-menthane framework. However, these compounds are known to be racemic mixtures. The cooling sensates of the present invention also contain the p-menthane framework. However, unlike the known cooling sensates, the present inventions are enantiomers. Compounds were discovered that have excellent cool/refreshing properties and are long lasting, compared with the well-known compounds ℓ -menthol and menthoxypropane-1,2-diol.

[0026] Example 1 describes the preparation of (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol, a compound of the present invention where n=2.

[0027] Example 2 describes the preparation of (1'R, 2'S, 5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol, a compound of the present invention where n=3.

[0028] Example 3 describes the preparation of (1'R, 2'S, 5'R)-4-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol where n=4.

[0029] As described above, the compounds of the present invention, as exemplified by synthesis of (1'R, 2'S, 5'R)-3- ℓ -menthoxypropan-1-ol, can be obtained through easily obtained raw materials, through short processes, and without complicated operations.

[0030] The compounds of the present invention have low volatility and are very nearly odorless liquids. They have an unexpectedly superior cooling and/or refreshing effect of long-lasting duration. The compounds of the present invention can be added to and used in a variety of flavor formulations, in formulations for the mouth, in food and beverage products, and in toiletry products.

[0031] Although it depends on the objective and the type of flavor formulation, when using the compound of the present invention in various flavor formulations, it is normally mixed in from about 0.001 to about 95 % by weight of the overall flavor formulation. The preferred range is from about 0.001 to about 30 % by weight. For use in mouth formulations, such as, but not limited to, paste toothpaste, powder toothpaste, gel toothpaste and chewing gum, the present invention is combined from about 0.001 to about 25 % by weight of the overall mouth formulation. The preferred range is from about 0.01 to about 15 % by weight.

[0032] For use in food and beverage products, such as, but not limited to, fruit juices, fruit wines, dairy drinks, carbonated drinks, a sports beverage, ice cream, sherbet, ice candy, jelly and hard candy, the present invention is combined from about 0.001 to about 25% by weight of the flavor formulation of the food and beverage product. The preferred range is from about 0.01 to about 15 % by weight.

[0033] For use in toiletries, such as, but not limited to, eau de toilette, lotion, milky lotion, facial creams, facial packs, hair toiletries, shampoos, face cleansers, anti-perspirants, and deodorants, the present invention is combined from about 0.0001 to about 20 % by weight of the flavor formulation of the toiletry product. The range is preferably from about 0.001 to about 10 % by weight, and more preferably from about 0.01 to about 10 % by weight.

[0034] In these flavor formulations, mouth formulations, food and beverage products, and toiletries, appropriate components other than the compound of the present invention can be freely chosen. The selection of these additional components will be apparent to one of ordinary skill in the art.

[0035] For example, for a facial cream, additional ingredients such as an emulsifier, fragrance, antiseptic agents, pigments, nutritive agents, moisturizers and ultraviolet protection can be selected and blended using standard methods. Similarly, eau de toilette, lotion, milky lotion, facial packs, hair care products, soap, anti-perspirants, deodorizers can also have varying components selected and as required depending on the type of product.

[0036] Analysis of the examples was conducted by using the following analytical equipment under specified conditions:

Column chromatogram: 5890-A (Hewlett-Packard Company);

Column: Chemical Bounded Column OV-1 25 mm x 0.25 mm ID 0.15 Mm (GL Science Company);

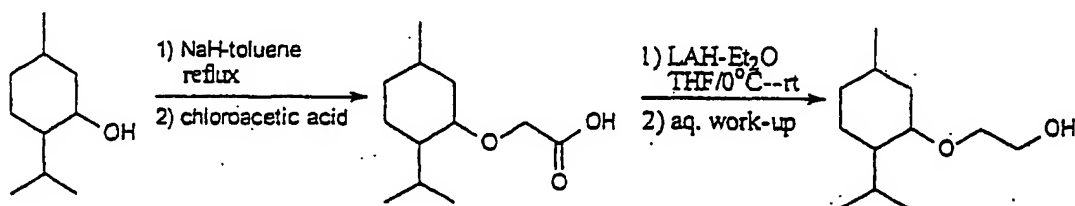
Temperature: 70-220 degrees C (heated at 4°C/minute);

Degree of optical rotation: DIP-370 model (Japan Spectral Industry Company).

Comparative Example 1

Preparation of (d,l)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol

[0037]



Preparation of (d,l)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]acetic acid

[0038] (d,l)-2-[5'-Methyl-2'-(methylethyl)cyclohexyloxy]acetic acid was prepared from (d,l)-menthol as described in the literature (*Org. Syn. Coll. Vol. III*, p. 544), with sodium hydride being used in place of sodium metal. From (d,l)-menthol (20.0 g, 0.128 moles) was obtained (d,l)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]acetic acid (20.05 g, 73.2% yield).

[0039] The CAS registry number is 71420-37-6. The molecular formula is $C_{12}H_{22}O_3$ and the molecular weight is 214.30. The boiling point is 109°C at 0.38 mm Hg.

[0040] 500 MHz 1H -NMR analysis in $CDCl_3$ provided the following data: δ 0.76 (d, 3H), 0.79-1.0 (m, 3H), 0.88 (d, 3H), 0.90 (d, 3H), 1.26-1.38 (m, 2H), 1.59-1.67 (m, 2H), 2.01-2.06 (m, 1H), 2.16-2.20 (m, 1H), 3.18 (dt, 1H), 4.07 (d, 1H), 4.18 (d, 1H), 9.70 (bs, 1H).

[0041] 125 MHz ^{13}C -NMR analysis in $CDCl_3$ provided the following data: δ 16.14, 20.88, 22.16, 23.19, 25.63, 31.45, 34.27, 39.87, 47.92, 65.42, 80.63, 174.59.

[0042] IR analysis provided the following data ($\nu_{max}(cm^{-1})$): 3060 (m), 2950 (s), 1760(s), 1460(m), 1240 (w), 1120(s).

[0043] MS analysis provided the following data (m/z): 155 (M-59) $^+$, 143, 138, 129, 123, 115, 109, 95, 81, 71, 55, 41.

Preparation of (d,l)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol

[0044] A 1.0 M solution of LAH- Et_2O (32.7 ml) was added drop-wise to an ice cold stirred solution of (d,l)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]acetic acid (8.0 g, 0.037 moles) in 200 ml of anhydrous THF. After addition the mixture was allowed to warm to room temperature with continued stirring for 6h. Water (1 ml) is cautiously added drop-

wise, followed by the drop-wise addition of 3.0 M NaOH (1 ml) and water (3.0 ml). This mixture was stirred at room temperature for 1 hr, followed by transfer to a separatory funnel. The organic layer was separated and washed successively with 10% HCl, sat. NaHCO₃, and brine, followed by drying over MgSO₄. After solvent removal under reduced pressure, the pale yellow oil was distilled under vacuum to give (*d, l*)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol (5.5g, 73.3% yield).

[0045] The CAS registry number is 38618-23-4. The molecular formula is C₁₂H₂₄O₂ and the molecular weight is 200.32. The boiling point is 70°C at 0.5 mm Hg.

[0046] 500 MHz ¹H-NMR analysis in CDCl₃ provided the following data: δ 0.76 (d, 3H), 0.79-0.86 (m, 2H), 0.88 (d, 3H), 0.90 (d, 3H), 0.92-1.00 (m, 2H), 1.20-1.24 (m, 1H), 1.29-1.38 (m, 1H), 1.58-1.66 (m, 2H), 2.05-2.10 (m, 1H), 2.12-2.20 (m, 2H), 3.06 (dt, 1H), 3.37-3.42 (m, 1H), 3.65-3.72 (m, 3H).

[0047] 125 MHz ¹³C-NMR analysis in CDCl₃ provided the following data: δ 16.21, 20.92, 22.28, 23.35, 25.76, 31.51, 34.52, 40.45, 48.26, 62.27, 69.39, 79.54.

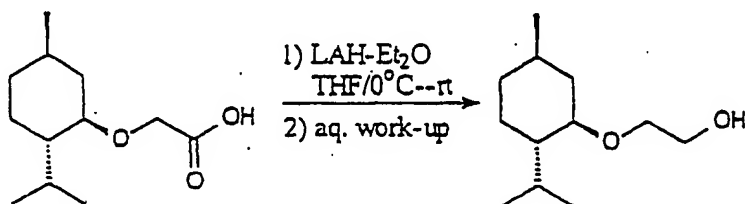
[0048] IR analysis provided the following data (ν_{max}(cm⁻¹)): 3425 (m), 2950 (s), 1460(m), 1340 (w), 1110(s), 1050(s).

[0049] MS analysis provided the following data (m/z): 200 (M⁺), 185, 169, 157, 138, 123, 115, 95, 81, 71, 55, 41.

Example 1

Preparation of (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol

[0050]



Preparation of (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl) cyclohexyloxy] acetic acid

[0051] (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]acetic acid was purchased from Aldrich Chemical Co. and was used without further purification. Alternatively, (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy] acetic acid can be prepared as described in the literature from *l*-menthol (*Org.Syn.Coll.Vol.III*, p. 544), or as described above for the preparation of (*d, l*)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy] acetic acid.

Preparation of (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol

[0052] A 1.0 M solution of LAH-Et₂O (37 ml) was added drop-wise to an ice cold stirred solution of (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]acetic acid (8.0 g, 0.037 moles) in 200 ml of anhydrous THF. After addition the mixture was allowed to warm to room temperature with continued stirring for 6h. Water (1 ml) was cautiously added drop-wise, followed by the drop-wise addition of 3.0 M NaOH (1 ml) and water (3.0 ml). This mixture was stirred at room temperature for 1 hr, followed by transfer to a separatory funnel. The organic layer was separated and washed successively with 10% HCl, sat. NaHCO₃, and brine, followed by drying over MgSO₄. After solvent removal under reduced pressure, the pale yellow oil was distilled under vacuum to give (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl) cyclohexyloxy]ethan-1-ol (6.4g, 85.7% yield).

[0053] The CAS registry number is 75443-64-0. The molecular formula is C₁₂H₂₄O₂ and the molecular weight is 200.32. The boiling point is 70°C at 0.5 mm Hg.

[0054] 500 MHz ¹H-NMR analysis in CDCl₃ provided the following data: δ 0.76 (d, 3H), 0.79-0.86 (m, 2H), 0.88 (d, 3H), 0.90 (d, 3H), 0.92-1.00 (m, 2H), 1.20-1.24 (m, 1H), 1.29-1.38 (m, 1H), 1.58-1.66 (m, 2H), 2.05-2.10 (m, 1H), 2.12-2.20 (m, 2H), 3.06 (dt, 1H), 3.37-3.42 (m, 1H), 3.65-3.72 (m, 3H).

[0055] 125 MHz ¹³C-NMR analysis in CDCl₃ provided the following data: δ 16.29, 21.00, 22.35, 23.44, 25.84, 31.59, 34.60, 40.52, 48.34, 62.35, 69.47, 79.61.

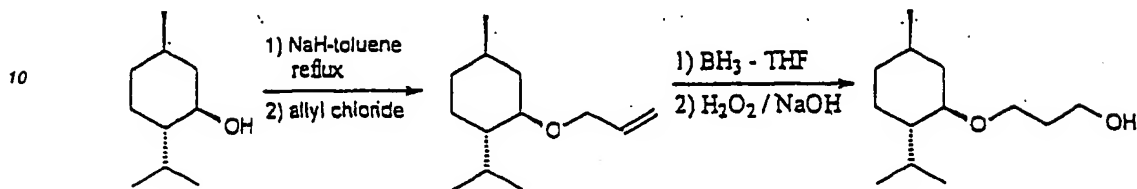
[0056] IR analysis provided the following data (ν_{max}(cm⁻¹)): 3410 (m), 2950 (s), 1460(m), 1340 (w), 1110(s), 1050(s).

[0057] MS analysis provided the following data (m/z): 200 (M⁺), 185, 169, 157, 138, 123, 115, 95, 81, 71, 55, 41.

Example 2

Preparation of (1'R, 2'S, 5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol

[0058]



Preparation of (1'R, 2'S, 5'R)-1-[5'-methyl-2'-(methylethyl)cyclohexyloxy]prop-2-ene

[0059] To a solution of *l*-menthol (30.0g, 0.19 moles) in anhydrous toluene (300 ml) was added sodium hydride (11.5g, 0.29 moles) in several small portions. The reaction flask was equipped with a water-cooled reflux condenser and the mixture was vigorously refluxed for 72 hours. The reaction vessel was allowed to cool to room temperature and allyl bromide (32.6g, 0.27 moles) was added drop-wise over 1hr. The resulting mixture was gently refluxed for 3hr, cooled to room temperature, and the excess sodium hydride was decomposed with careful drop-wise addition of water. The organic layer was separated and washed successively with 10% HCl, sat. NaHCO₃, and brine, followed by drying over anhydrous MgSO₄. After solvent removal under reduced pressure, the pale yellow oil was distilled under vacuum to give (1'R, 2'S, 5'R)-1-[5'-methyl-2'-(methylethyl)cyclohexyloxy]prop-2-ene (34.3g, 92% yield).

[0060] The CAS registry number is 67528-21-6. The molecular formula is C₁₃H₂₄O and the molecular weight is 196.33. The boiling point is 56°C at 1.0 mm Hg.

[0061] 500 MHz ¹H-NMR analysis in CDCl₃ provided the following data: δ 0.76 (d, 3H), 0.88 (d, 3H), 0.90 (d, 3H), 0.79-1.00 (m, 3H), 1.19-1.26 (m, 1H), 1.28-1.37 (m, 1H), 1.57-1.66 (m, 2H), 2.05-2.10 (m, 1H), 2.18-2.25 (m, 1H), 3.06 (dt, 1H), 3.84-3.90 (m, 1H), 4.08-4.14 (m, 1H), 5.10-5.13 (m, 1H), 5.22-5.27 (m, 1H), 5.88-5.96 (m, 1H).

[0062] 125 MHz ¹³C-NMR analysis in CDCl₃ provided the following data: δ 16.33, 21.02, 22.40, 23.49, 25.64, 31.62, 34.64, 40.59, 48.36, 69.58, 78.80, 116.31, 135.83.

[0063] IR analysis provided the following data (ν_{max}(cm⁻¹)): 3080(w), 2960(s), 2940(s), 2875(s), 1735(w), 1650(w), 1460(m), 1375(m), 1090(m), 920(m).

[0064] MS analysis provided the following data (m/z): 196 (M⁺), 181, 167, 138, 123, 111, 95, 81, 69, 55, 41.

Preparation of (1'R, 2'S, 5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol

[0065] A 1M solution of BH₃-THF (32 ml) was added drop-wise to a stirred solution of (1'R, 2'S, 5'R)-1-[5'-methyl-2'-(methylethyl)cyclohexyloxy]prop-2-ene (11.5g, 0.06 moles) in 100 ml of anhydrous THF at room temperature under nitrogen. After stirring at room temperature for 1hr, water (15 ml) was added drop-wise followed by the addition of 20 ml of 3M NaOH. Hydrogen peroxide (30% aq., 20 ml) was added drop-wise such that the temperature remains between 30-50 C. When the addition was complete, stirring was continued for 1h. Fresh diethyl ether (100 ml) was added to the reaction mixture, which was sequentially washed with ice water (2X) and brine, followed by drying over MgSO₄. After solvent removal under reduced pressure, the pale yellow oil was distilled under vacuum to give (1'R, 2'S, 5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol (8.7g, 70.2% yield).

[0066] The molecular formula is C₁₃H₂₆O₂ and the molecular weight is 214.34. The boiling point is 80°C at 0.42 mm Hg.

[0067] 500 MHz ¹H-NMR analysis in CDCl₃ provided the following data: δ 0.76 (d, 3H), 0.82 (m, 1H), 0.87 (d, 3H), 0.91 (d, 3H), 0.94 (m, 1H), 1.18 (m, 1H), 1.32 (m, 1H), 1.60 (m, 2H), 1.80 (m, 2H), 2.11 (m, 2H), 2.24 (bs, 1H), 3.01 (m, 1H), 3.48 (m, 1H), 3.76 (t, 3H), 3.80 (m, 1H).

[0068] 125 MHz ¹³C-NMR analysis in CDCl₃ provided the following data: δ 16.30, 21.01, 22.36, 23.44, 25.86, 31.62, 32.53, 34.61, 40.40, 48.34, 62.48, 67.92, 79.85.

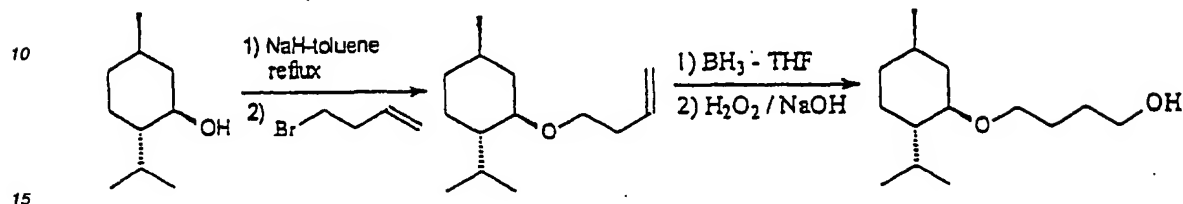
[0069] IR analysis provided the following data (ν_{max}(cm⁻¹)): 3380 (m), 2950(s), 1460 (w), 1110 (m), 1090 (m).

[0070] MS analysis provided the following data (m/z): 214 (M⁺), 199, 171, 155, 138, 129, 123, 95, 81, 71, 55, 41.

Example 3

Preparation of (1'R, 2'S, 5'R)-4-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol

[0071]



Preparation of (1'R, 2'S, 5'R)-1-[5'-methyl-2'-(methylethyl)cyclohexyloxy]but-3-ene

[0072] To a solution of *l*-menthol (23.1g, 0.148 moles) in anhydrous toluene (300 ml) was added sodium hydride (60% in mineral oil dispersion; 6.2g, 0.155 moles) in several small portions. The reaction flask was equipped with a water-cooled reflux condenser and the mixture was vigorously refluxed for 18 hours. The reaction vessel was allowed to cool to room temperature and 4-bromo-1-butene (10.0g, 0.074 moles) was added drop-wise over 1 hr. The resulting mixture was gently refluxed for 6 hr, cooled to room temperature, and the excess sodium hydride decomposed with careful drop-wise addition of water. The organic layer was separated and washed successively with 10% HCl, sat. NaHCO₃, and brine, followed by drying over MgSO₄. After solvent removal under reduced pressure, the pale yellow

was purified by flash chromatography (1:4; EtOAc:hexane) to give (1'R, 2'S, 5'R)-1-[5'-methyl-2'-(methylethyl)cyclohexyloxy]but-3-ene (1.4g, 4.5 % yield).

[0073] The molecular formula is C₁₄H₂₆O and the molecular weight is 210.36.

[0074] 500 MHz ¹H-NMR analysis in CDCl₃ provided the following data: δ 0.76 (d, 3H), 0.88 (d, 3H), 0.90 (d, 3H), 0.79-1.00 (m, 3H), 1.19-1.26 (m, 1H), 1.28-1.37 (m, 1H), 1.58-1.66 (m, 2H), 2.05-2.17 (m, 1H), 2.17-2.24 (m, 1H), 2.28-2.32 (m, 2H), 3.00 (dt, 1H), 3.29-3.32 (m, 1H), 3.65-3.69 (m, 1H), 5.01 (dd, 1H), 5.07 (dd, 1H), 5.78-5.88 (m, 1H).

[0075] 125 MHz ¹³C-NMR analysis in CDCl₃ provided the following data: δ 16.38, 21.00, 22.41, 23.55, 25.67, 29.76, 31.65, 34.70, 40.60, 48.34, 68.04, 79.39, 116.06, 135.70.

[0076] IR analysis provided the following data (ν_{max}(cm⁻¹)): 3080(w), 2960(s), 2925(s), 2850(s), 1735(w), 1645(w), 1460(m), 1380(w), 1115(m), 1090(w), 915(w).

[0077] MS analysis provided the following data (m/z): 210 (M⁺), 195, 169, 139, 125, 95, 83, 69, 55, 41.

Preparation of (1'R, 2'S, 5'R)-4-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol

[0078] A 1M solution of BH₃-THF (2.85 ml) was added drop-wise to a stirred solution of (1'R, 2'S, 5'R)-1-[5'-methyl-2'-(methylethyl)cyclohexyloxy]but-3-ene (1.2g, 5.7 mmoles) in 10 ml of anhydrous THF at room temperature under nitrogen. After stirring at room temperature for 18hr, water (1 ml) was added drop-wise followed by the addition of 3M NaOH (1 ml). Hydrogen peroxide (30% aq., 1.0 ml) was added drop-wise such that the temperature remains between 30-50°C. When the addition was complete, stirring was continued for 1h. Fresh diethyl ether (20 ml) was added to the reaction mixture, which was sequentially washed with ice water (2X) and brine, followed by drying over MgSO₄. After solvent removal under reduced pressure, the pale yellow oil was purified by flash chromatography (1:4; EtOAc:hexane) to give (1'R, 2'S, 5'R)-4-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol (0.45g, 35% yield).

[0079] The molecular formula is C₁₄H₂₈O₂ and the molecular weight is 228.37. The boiling point is 98°C at 0.30 mm Hg.

[0080] 500 MHz ¹H-NMR analysis in CDCl₃ provided the following data: δ 0.76 (d, 3H), 0.78-1.00 (m, 3H), 0.88 (d, 3H), 0.90 (d, 3H), 1.18-1.24 (m, 1H), 1.28-1.40 (m, 1H), 1.52-1.74 (m, 6H), 2.06-2.12 (m, 1H), 2.14-2.20 (m, 1H), 2.53 (bs, 1H), 3.01 (dt, 1H), 3.30-3.36 (m, 1H), 3.59-3.66 (m, 3H).

[0081] 125 MHz ¹³C-NMR analysis in CDCl₃ provided the following data: δ 16.38, 20.99, 22.35, 23.52, 25.79, 27.52, 30.52, 31.65, 34.61, 40.48, 48.31, 62.86, 68.47, 79.59.

[0082] IR analysis provided the following data (ν_{max}(cm⁻¹)): 3360(m), 2960(s), 2870(s), 1460(m), 1370(w), 1180(w), 1110(m), 1060(m).

[0083] MS analysis provided the following data (m/z): 228 (M⁺), 155, 138, 123, 95, 89, 81, 71, 55, 41.

Embodiment 1 - Paste Toothpaste

[0084] The ingredients listed below were mixed in a suitable mixing apparatus to make paste toothpaste.

Ingredient	Weight Percent
Calcium hydrogen phosphate	51.0
Glycerin	26.0
Purified water	19.39
Sodium lauryl sulfate	1.4
Sodium carboxymethyl cellulose	1.0
Sodium saccharin	0.15
Sodium benzoate	0.05
Toothpaste flavor	1.0
Compound of Example 2	0.01
Total	100.0

[0085] Users of the powder toothpaste as prepared above, reported experiencing a cool/refreshing feeling in the mouth. There was no bitterness. The clean, cooling/refreshing sensation was long lasting and is a positive signal of effectiveness.

Embodiment 2 - Gel Toothpaste

[0086] The ingredients listed below were mixed in a suitable mixing apparatus to prepare a gel toothpaste.

Ingredient	Weight Percent
sodium bicarbonate	97.69
magnesium oxide	0.50
flavor	1.00
Compound of Example 2	0.01
polyethylene glycol	0.50
sodium saccharin	0.20
sodium triphosphate	0.10
Total	100.0

[0087] Users of this gel toothpaste reported experiencing a cool/refreshing feeling in the mouth. There was no bitterness. The clean, cooling/refreshing sensation was long lasting and is a positive signal of effectiveness.

Embodiment 3 - Chewing Gum

[0088] A chewing gum was prepared by first heating and melting the gum base in a high shear gum mixer. The corn syrup, glycerin and half the 10X sugar were added to the gum. The mixture was heated and stirred while the remainder of the sugar was added. Then, the flavor and the compound of the present invention were added until the mixture was uniform. As a final step, the uniform mixture was rolled out on a marble slab and cut into appropriate sizes.

Ingredient	Weight Percent
gum base	24.0
corn syrup 42DE	6.7

(continued)

Ingredient	Weight Percent
Glycerin	1.1
10X sugar	67.19
Chewing gum flavor	1.0
Compound of Example 2	0.01
Total	100.0

[0089] The chewing gum as prepared above had a cool/refreshing feeling with no bitterness. Compared to chewing gum which did not use a compound of the present invention, the chewing gum as prepared above had a longer lasting cool/refreshing flavor with an impression of a prolonged flavor impact.

Embodiment 4 - Hard Candy

[0090] A hard candy was prepared by combining all the ingredients listed below in a copper kettle. The color, flavor ("Cider flavor E-7004" Takasago International Corporation) and acid were mixed well, heated and melted at 230°F. The final mixture was poured into molds and allowed to cool.

Ingredient	Weight Percent
Sugar	51.9
Water	12.1
Corn Syrup 42DE	34.6
Caramel Color	0.89
Flavor - Cider Flavor E-7004	0.1
Citric Acid	0.4
Compound of Example 2	0.01
Total	100.0

[0091] Compared to hard candy which does not blend the compound of the present invention, there was a marked refreshing, longer lasting, non-bitter, coolness quality due to the inclusion of the compounds of the present invention.

Comparative Example

[0092] The enantiomeric compounds of the present invention, Examples 1 through 3 (E1, E2 and E3), were tested against the prior art racemic mixture of 2-[5'-methyl-2'-(methylethyl)-cyclohexyloxy]ethan-1-ol (C1). Six evaluators swished 10 ml of a 150 ppm solution of each compound for 15 seconds and spat out. The quality of the flavor and cooling characteristics were reported at various intervals after spitting out. The results are summarized in the following table:

	Compound Name	1-5 Minutes	10-15 Minutes	30 Minutes
C1	2-[5'-methyl-2'-(methylethyl)-cyclohexyloxy]ethan-1-ol	initially slightly cool, builds to medium intensity at 5 min., non-mentholic and bitter flavor	cooling intensity decreasing, lasting 10-15 min.	no cooling
E1	(1'R,2'S,5'R)-2-[5'-methyl-2'-(methylethyl)-cyclohexyloxy]ethan-1-ol	initially slightly cool, clean, slight bitter and mentholic taste, cooling increased at 3-4 mins.	Peak cool at 15 min., clean, pleasant, non-medicinal	cooling

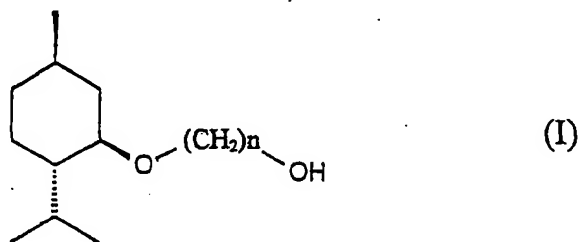
(continued)

	Compound Name	1-5 Minutes	10-15 Minutes	30 Minutes
5	E2 (1'R,2'S,5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol	immediately cool, very clean, very slight medicinal and bitter, good good at 1 min.	Peak cool at 10-13 mins., clean, fresh, non-mentholic	strong cooling 30+ min.
10	E3 (1'R,2'S,5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol	slight immediate cool, initial bitter and medicinal taste, cooling increases from 3-5 mins.	Peak cool at 7 mins., «tingling» cool sensation	cooling

15 [0093] The single enantiomer compounds of the present invention provide a cool/refreshing feeling. Compared with known compounds, they have a longer lasting cooling/refreshing effect. Since food, beverage, cosmetic and other products containing a compound of the present invention have longer lasting cooling and refreshing properties, the value of these products is increased.

Claims

1. A cooling sensate compound having the general formula (I):



wherein n is an integer from 2 to 6.

2. A cooling sensate compound according to claim 1, wherein said 3-*l*-menthoxyalkan-1-ol is (1'R, 2'S, 5'R)-2-[5'-methyl-2'-(methylethyl)cyclohexyloxy]ethan-1-ol.
3. A cooling sensate compound according to claim 1, wherein said 3-*l*-menthoxyalkan-1-ol is (1'R,2'S,5'R)-3-[5'-methyl-2'-(methylethyl)cyclohexyloxy]propan-1-ol.
4. A cooling sensate compound according to claim 1, wherein said 3-*l*-menthoxyalkan-1-ol is (1'R,2'S,5'R)-4-[5'-methyl-2'-(methylethyl)cyclohexyloxy]butan-1-ol.
5. A cooling sensate composition comprising a 3-*l*-menthoxyalkan-1-ol compound as defined by any one of claims 1 to 4, and a suitable carrier.
6. A cooling sensate composition according to claim 5, whereby said cooling sensate composition is effective to act as at least one of a food additive, a beverage additive, a flavor additive and a toiletry additive.
7. A cooling sensate composition according to claim 5 or 6, whereby said cooling sensate composition is effective to act as at least one of a fruit juice, a fruit wine, a dairy drink, a carbonated drink, a sports beverage, an ice cream, a sherbet, an ice candy, a jelly, a hard candy, a chewing gum, a bubble gum, a pressed mint tablet, a mouth wash, a toothpaste, a tooth gel, a cough drop, a nebulizer, a perfume, an eau de toilette, a cologne, an after shave, a deodorant, an antiperspirant, a hand cream, a shampoo and a soap.

8. A cooling sensate composition according to any one of claims 5 to 7, further comprising at least one additional sensate material, said at least one additional sensate material being effective to provide at least one of a warming, tingling, numbing, cooling, sweetness, bitterness, masking, flavor enhancing, pungency, or ethanolic sensation.

5 9. A method of using a compound according to any one of claims 1 to 4 as a cooling sensate, comprising:
adding an effective amount of a compound of formula (I) to at least one of a food additive, a beverage additive, a flavor additive, and a toiletry additive.

10 10. A method according to claim 9, wherein said at least one of said food additive, said beverage additive, said flavor additive, and said toiletry additive is selected from the group consisting of a fruit juice, a fruit wine, a dairy drink, a carbonated drink, a sports beverage, an ice cream, a sherbet, an ice candy, a jelly, a hard candy, a chewing gum, a bubble gum, a pressed mint tablet, a mouth wash, a toothpaste, a tooth gel, a cough drop, a nebulizer, a perfume, an eau de toilette, a cologne, an after shave, a deodorant, an antiperspirant, a hand cream, a shampoo and a soap.

15

20

25

30

35

40

45

50

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 40 0267

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	GB 1 315 626 A (WILKINSON SWORD LTD) 2 May 1973 (1973-05-02) * page 1, line 9 - line 39 * * page 2, line 67 - line 70 * * page 2, line 100 - line 121 * ---	1-10	C07C35/08 A61K7/16 A23L1/22
X	KYOJI FURUTA ET AL: "A direct synthesis of cyclic acetals from beta- or gamma-hydroxy ethers by means of C-H activation" TETRAHEDRON LETTERS., vol. 29, no. 18, 1988, pages 2215-18, XP002168520 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 * table 1, compound 4 * ---	1,2	
A	US 4 029 759 A (D AUDIFFRET YVES TOLLARD ET AL) 14 June 1977 (1977-06-14) * column 1, line 1 - line 54 * * claim 1 * -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07C A61K A23L
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 29 May 2001	Examiner O'Sullivan, P
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03 82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 40 0267

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

29-05-2001

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 1315626	A	02-05-1973	NONE	

US 4029759	A	14-06-1977	AT 331415 B	25-08-1976
			AT 169273 A	15-11-1975
			AU 466320 B	23-10-1975
			AU 5251473 A	22-08-1974
			BE 795751 A	21-08-1973
			CA 1007108 A	22-03-1977
			CH 578841 A	31-08-1976
			DE 2309256 A	13-09-1973
			FR 2174104 A	12-10-1973
			GB 1422272 A	21-01-1976
			JP 48098012 A	13-12-1973
			LU 64851 A	04-09-1973
			NL 7302675 A	30-08-1973
			NO 137476 B	28-11-1977

EPO FORM P0489

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82